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(54) **Sustained release formulation comprising octreotide and two or more polylactide-co-glycolide polymers**

Zusammensetzung mit verzögerter Freisetzung enthaltend octreotide und zwei oder mehr polylactide-co-glycolide polymere

Composition à libération prolongée comprenant octreotide et deux ou plus polymères de polylactide-co-glycolide

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(73) Proprietor: **Novartis AG**
4056 Basel (CH)

(72) Inventors:
• **Petersen, Holger**
79591, Eimeldingen (DE)

• **Ahlheim, Markus**
79219, Staufen (DE)

(74) Representative: **Gruber, Markus**
Novartis Pharma AG
Patent Department
4002 Basel (CH)

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Description

[0001] The present invention relates to sustained release formulations comprising as active ingredient octreotide or a pharmaceutically-acceptable salt thereof and two or more different polylactide-co-glycolide polymers (PLGAs).

[0002] These pharmaceutical compositions according to the present invention are indicated for inter alia long-term maintenance therapy in acromegalic patients, and treatment of severe diarrhea and flushing associated with malignant carcinoid tumors and vasoactive intestinal peptide tumors (vipoma tumors).

[0003] Peptide drugs are usually administered systemically, e.g. parenterally. However, parenteral administration may be painful and cause discomfort, especially for repeated daily administrations. In order to minimize the number of injections to a patient, the drug substance should be administered as a depot formulation. A common drawback with injectable depot formulations is the fluctuation in plasma levels such as high peak levels together with plasma levels close to zero during the entire release period.

[0004] The present invention discloses a sustained release formulation comprising as active ingredient (drug substance) octreotide or a pharmaceutically-acceptable salt thereof. Octreotide (US 4,395,403) is a somatostatin analog having the following formula:



[0005] The active ingredient may be in the form of a pharmaceutically acceptable salt of octreotide, such as an acid addition salt with e.g. inorganic acid, polymeric acid or organic acid, for example with hydrochloric acid, acetic acid, lactic acid, citric acid, fumaric acid, malonic acid, maleic acid, tartaric acid, aspartic acid, benzoic acid, succinic acid or pamoic (embonic) acid. Acid addition salts may exist as mono- or divalent salts, e.g. depending whether 1 or 2 acid equivalents are added. Preferred is the pamoate monosalt of octreotide.

[0006] The particle size distribution of the drug substance influences the release profile of the drug from the depot form. The drug substance which is used to prepare the depot formulation is crystalline or in the form of an amorphous powder. Preferred is an amorphous powder which has a particle of a size of about 0.1 microns to about 15 microns (99% > 0.1 microns, 99% < 15 microns), preferably from 1 to less than about 10 microns (90% > 1 microns, 90% < 10 microns). The drug substance preferentially undergoes a micronization process to present the required particle size distribution.

[0007] The present disclosure further provides a sustained release pharmaceutical composition (depot) comprising as active ingredient octreotide or a pharmaceutically-acceptable salt thereof incorporated in blends or mixtures of poly(lactide-co-glycolide)s (PLGAs), for instance in form of microparticles.

[0008] Alternatively to blends of PLGAs, in an aspect of the present invention the pharmaceutical composition comprises a mixture of PLGA polymers containing the active ingredient; i.e. the active ingredient may be incorporated into one or more PLGAs in form of microparticles, and is then mixed with another microparticle formulation also comprising the active ingredient and one or more PLGAs.

[0009] The pharmaceutical composition according to the present invention allows a sustained release of the active ingredient over a period of more than three month, preferentially between three and six months. During the release of the active ingredient the plasma levels of octreotide are within the therapeutic range. It is understood that the exact dose of octreotide will depend on a number of factors, including the condition to be treated, the severity of the condition to be treated, the weight of the subject and the duration of therapy.

[0010] Surprisingly fluctuations in plasma levels can significantly be reduced by using a suitable combination of 2 or more different PLGAs in the pharmaceutical composition according to the present invention.

[0011] The drug substance is incorporated into a biodegradable polymer matrix consisting of 2 or more different polylactide-co-glycolide polymers (PLGAs). The PLGAs have a lactide: glycolide monomer ratio of 100:0 to 40:60, preferably 90:10 to 40:60, more preferably 85:15 to 65:35. A PLGA having a lactide:glycolide monomer ratio of 100:0, i.e. containing no glycolide monomer, is a polylactide (PLA) which is also included in the definition of PLGA according to the present invention.

[0012] The PLGAs according to the present invention have a molecular weight (Mw) ranging from 1,000 to 500,000 Da, preferably from 5,000 to 100,000 Da. The architecture of the polymers can be linear, branched, hyperbranched, comb-like branched, dendrimer-like branched, T-shaped or a star-shaped polymer of the above building blocks. In a preferred embodiment of the present invention at least two PLGAs in the pharmaceutical composition are linear.

[0013] An example of a star polymer is an ester of a polyol which contains at least 3 hydroxy groups which are converted into poly(lactide-co-glycolide) chains. The polyol is preferably a saccharide, most preferably glucose.

[0014] The inherent viscosity (IV) of the PLGAs according to the present invention is below 0.9 dl/g in chloroform, preferentially below 0.8 dl/g in chloroform. The inherent viscosities can be measured by the conventional methods of

flow time measurement, as described for example in "Pharmacopée Européenne", 1997, pages 17-18 (capillary tube method). Unless stated otherwise, these viscosities have been measured in chloroform at a concentration of 0.5% at 25°C or in hexaiso fluoropropanol at a concentration of 0.5% at 30°C.

[0015] End groups of the PLGAs according to the present invention can be but are not limited to hydroxy, carboxyl, ester or the like.

[0016] The drug substance content of the depot formulation (the loading) is in a range of 1% to 30%, preferred 10% to 25%, more preferred 15% to 20%. The loading is defined as the weight ratio of drug substance as free base to the total mass of the PLGA formulation.

[0017] Suitable polymers are commonly known but not limited to those commercially available as RESOMER® by Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany, LACTEL® by Absorbable Polymers International (API) Pelham, AL, USA / DURECT Corp., Cupertino, CA, USA, MEDISORB® by Alkermes, Inc., Cambridge, MA, USA, PURASORB® by PURAC biochem BV, Gorinchem, The Netherlands. Examples of suitable polymers are listed in Table 1.

Table 1: Examples of suitable polymers

No	Product name	Polymer	Inherent viscosity [dL/g]	Producer Supplier
1	D,L-POLYMI/D-GLUCOSE	Star-branched Poly(D,L-lactide-co-glycolide) 50:50 / D-Glucose	0.29 - 0.35	Novartis
2	Resomer® R 202 H	Linear Poly(D,L-lactide) free carboxylic acid end group	0.16 - 0.24 ¹⁾	Boehringer
3	Resomer® R 202 S	Linear Poly(D,L-lactide)	0.16 - 0.24 ¹⁾	Boehringer
4	Resomer® R 203 S	Linear Poly(D,L-lactide)	0.25 - 0.35 ¹⁾	Boehringer
5	Resomer® RG 752 H	Linear Poly(D,L-lactide-co-glycolide) 75:25 free carboxylic acid end group	0.14 - 0.22 ¹⁾	Boehringer
5a	Resomer® RG 752 S	Linear Poly(D,L-lactide-co-glycolide) 75:25	0.16 - 0.24 ¹⁾	Boehringer
6	Resomer® CR RG 75:25 or Resomer® RG Type 75:25 S / Resomer® RG 753 S	Linear Poly(D,L-lactide-co-glycolide) 75:25	0.32 - 0.44 ¹⁾	Boehringer
7	Lactel® 100D020A	Linear Poly(D,L-lactide) free carboxylic acid end group	0.15 - 0.25 ²⁾	API/Durect
8	Lactel® 100D040A	Linear Poly(D,L-lactide) free carboxylic acid end group	0.26 - 0.54 ²⁾	API/Durect
9	Lactel® 100D040	Linear Poly(D,L-lactide)	0.26 - 0.54 ²⁾	API/Durect
10	Lactel® 100D065	Linear Poly(D,L-lactide)	0.55 - 0.75 ²⁾	API/Durect
11	Lactel® 85DG040	Linear Poly(D,L-lactide-co-glycolide) 85:15	0.26 - 0.54 ²⁾	API/Durect
12	Lactel® 85DG065	Linear Poly(D,L-lactide-co-glycolide) 85:15	0.55 - 0.75 ²⁾	API/Durect
13	Lactel® 75DG065	Linear Poly(D,L-lactide-co-glycolide) 75:25	0.55 - 0.75 ²⁾	API/Durect
14	Lactel® 65DG065	Linear Poly(D,L-lactide-co-glycolide) 65:35	0.55 - 0.75 ³⁾	API/Durect
15	Lactel® 50DG065	Linear Poly(D,L-lactide-co-glycolide) 50:50	0.55 - 0.75 ³⁾	API/Durect
16	Medisorb® 100 DL HIGH IV	Linear Poly(D,L-lactide)	0.66 - 0.80	Alkermes
17	Medisorb® 100 DL LOW IV	Linear Poly(D,L-lactide)	0.50 - 0.65	Alkermes

(continued)

No	Product name	Polymer	Inherent viscosity [dL/g]	Producer Supplier
18	Medisorb® 8515 DL HIGH IV	Linear Poly(D,L-lactide-co-glycolide) 85:15	0.66 - 0.80	Alkermes
19	Medisorb® 8515 DL LOW IV	Linear Poly(D,L-lactide-co-glycolide)85:15	0.50 - 0.65	Alkermes
20	Medisorb® 7525 DL HIGH IV	Linear Poly(D,L-lactide-co-glycolide) 75:25	0.66 - 0.80	Alkermes
21	Medisorb® 7525 DL LOW IV	Linear Poly(D,L-lactide-co-glycolide) 75:25	0.50 - 0.65	Alkermes
22	Medisorb® 6535 DL HIGH IV	Linear Poly(D,L-lactide-co-glycolide) 65:35	0.66 - 0.80	Alkermes
23	Medisorb® 6535 DL LOW IV	Linear Poly(D,L-lactide-co-glycolide) 65:35	0.50 - 0.65	Alkermes
24	Medisorb® 5050 DL HIGH IV	Linear Poly(D,L-lactide-co-glycolide) 50:50	0.66 - 0.80	Alkermes
25	Medisorb® 5050 DL LOW IV	Linear Poly(D,L-lactide-co-glycolide) 50:50	0.50 - 0.65	Alkermes
1) IV has been determined in chloroform at a concentration of 0.1 % at 25°C 2) IV has been determined in chloroform at a concentration of 0.5 g / dL at 30°C 3) IV has been determined in Hexafluoroisopropanol at a concentration of 0.5 g / dL at 30°C				

[0018] Plasma levels with low variability can be achieved over a time period of more than three month, preferentially between three and six month, only with pharmaceutical compositions according to the present invention, not with formulations containing only one single polymer from the table above.

[0019] In addition, the pharmaceutical composition according to the present invention can be manufactured aseptically or non-aseptically and sterilized terminally by gamma irradiation.

[0020] Preferred is terminal sterilization by gamma irradiation, resulting in a product with the highest sterility assurance possible.

[0021] The pharmaceutical composition according to the present invention may also contain one or more pharmaceutical excipients modulating the release behavior in an amount of 0.1% to 50%. Examples of such agents are: Poly(vinylpyrrolidone), carboxymethyl cellulose sodium (CMC-Na), dextrin, poly(ethyleneglycol), suitable surfactants such as poloxamers, also known as poly(oxyethylene-block-oxypropylene), Poly(oxyethylene)-sorbitan-fatty acid esters known and commercially available under the trade name TWEEN® (e.g. Tween 20, Tween 40, Tween 60, Tween 80, Tween 65 Tween 85, Tween 21, Tween 61, Tween 81), Sorbitan fatty acid esters e.g. of the type known and commercially available under the trade name SPAN, Lecithins, inorganic salts such as zinc carbonate, magnesium hydroxide, magnesium carbonate, or protamine, e.g. human protamine or salmon protamine, or natural or synthetic polymers bearing amine-residues such as polylysine .

[0022] The pharmaceutical composition according to the present invention is a depot mixture of different polymers in terms of compositions, molecular weight and/or polymer architectures. A polymer blend (reference) is defined herein as a solid solution or suspension of 2 or more different polymers in one microparticle. A mixture of depots (invention) in contrast is defined herein as a mixture of two or more depots like microparticles of different composition with one or more PLGAs in each depot.

[0023] The pharmaceutical composition according to the present invention can be in the form of microparticles. Preparation of microparticles comprising octreotide or a pharmaceutically-acceptable salt thereof is known and for instance disclosed in US5,445,832 or US5,538,739.

[0024] The microparticles according to the present invention may have a diameter from a few submicrons to a few millimeters, e.g. from about 0.01 microns to about 2 mm, e.g. from about 0.1 microns to about 500 microns. For pharmaceutical microparticles, diameters of at most about 250 microns, e.g. 10 to 200 microns, preferably 10 to 130 microns, more preferably 10 to 90 microns.

[0025] The microparticles according to the present invention may be mixed or coated with an anti-agglomerating agent or covered by a layer of an anti-agglomerating agent, e.g. in a prefilled syringe or vial. Suitable anti-agglomerating agents include, e.g. mannitol, glucose, dextrose, sucrose, sodium chloride, or water soluble polymers such as polyvinylpyrrolidone or polyethylene glycol, e.g. with the properties described above.

[0026] For microparticles according to the present invention in dry state preferably an anti-agglomerating agent is present in an amount of about 0.1 to about 10%, preferentially about 3% to 5%, e.g. about 4% by weight of the microparticles. A preferred anti-agglomerating agent in this respect is mannitol.

[0027] Alternatively, an anti-agglomerating agent can be applied to the microparticles during their manufacturing process. For example, at the step of filtering / washing the microparticles they can be additionally rinsed with an aqueous solution of an anti-agglomerating agent. Thus, a layer of the anti-agglomerating agent is formed on the surface of the microparticles. Preferably, the anti-agglomerating agent is present in the microparticles at an amount of less than 10%, more preferred less than 2%, most preferred less than 0.5% by weight of the microparticles. A preferred anti-agglomerating agent in this respect is mannitol.

[0028] The manufacturing process for the depot formulation of the current invention is described in more detail for microparticles:

The microparticles may be manufactured by several processes known in the art, e.g., coacervation or phase separation, spray drying, water-in-oil (W/O) or water-in-oil-in-water (W/O/W) or solids-in-oil-in-water (S/O/W) emulsion/suspension methods followed by solvent extraction or solvent evaporation. The emulsion/suspension method is the preferred process, which comprises the following steps:

(i) preparation of an internal organic phase comprising

(ia) dissolving the polymer or polymers in a suitable organic solvent or solvent mixture;
optionally dissolving/dispersing suitable additives;

(ib) dissolving/suspending/emulsification of the drug substance or an aqueous solution of the drug substance in the polymer solution obtained in step (ia);

(ii) Preparation of an external aqueous phase containing stabilizers and optionally but preferably buffer salts;

(iii) mixing the internal organic phase with the external aqueous phase e.g. with a device creating high shear forces, e.g. with a turbine or static mixer, to form an emulsion; and

(iv) hardening the microparticles by solvent evaporation or solvent extraction; washing the microparticles, e.g. with water; optionally rinse the microparticles with an aqueous solution of an anti-agglomerating agent, e.g. mannitol; collecting and drying the microparticles, e.g. freeze-drying or drying under vacuum, and sieving the microparticles through 140 μm .

[0029] Suitable organic solvents for the polymers include e.g. ethyl acetate, acetone, THF, acetonitrile, or halogenated hydrocarbons, e.g. methylene chloride, chloroform or hexafluoroisopropanol.

[0030] Suitable examples of a stabilizer for step (iib) include poly(vinylalcohol) (PVA), in an amount of 0.1 to 5%, hydroxyethyl cellulose (HEC) and/or hydroxypropyl cellulose (HPC), in a total amount of 0.01 to 5%, poly(vinyl pyrrolidone), Gelatin, preferably porcine or fish gelatin.

[0031] The dry microparticles composition can be terminally sterilized by gamma irradiation (overkill sterilization), optionally in bulk or after filling in the final container resulting in the highest sterility assurance possible. Alternatively the bulk sterilized microparticles can be resuspended in a suitable vehicle and filled as a suspension into a suitable device such as double chamber syringe with subsequent freeze drying.

[0032] The pharmaceutical composition according to the present invention containing microparticles may also contain a vehicle to facilitate reconstitution.

[0033] Prior to administration, the microparticles are suspended in a suitable vehicle for injection. Preferably, said vehicle is water based containing pharmaceutical excipients such as mannitol, sodium chloride, glucose, dextrose, sucrose, or glycerins, non-ionic surfactants (e.g. poloxamers, poly(oxyethylene)-sorbitan-fatty acid esters), carboxymethyl cellulose sodium (CMC-Na), sorbitol, poly(vinylpyrrolidone), or aluminium monostearate in order to ensure isotonicity and to improve the wettability and sedimentation properties of the microparticles. The wetting and viscosity enhancing agents may be present in an amount of 0.01 to 2%; the isotonicity agents are added in a suitable amount to ensure an isotonic injectable suspension.

[0034] The amount of liquid vehicle for suspension is preferably about 1 to 5 ml, e.g. 2 to 2.5 ml per dose. If desired the microparticles in dry form and the aqueous vehicle for reconstitution may be housed separately in a double chamber syringe.

[0035] The invention further provides the use of a pharmaceutical composition according to the present invention for inter alia long-term maintenance therapy in acromegalic patients, and treatment of severe diarrhea and flushing associated with malignant carcinoid tumors and vasoactive intestinal peptide tumors (vipoma tumors).

[0036] The utility of the pharmaceutical compositions according to the present invention can be shown in standard clinical or animal studies.

[0037] The invention further provides a kit comprising the depot formulation in a vial, optionally equipped with a transfer set, together with a water-based vehicle in an ampoule, vial or prefilled syringe or as microparticles and vehicle separated in a double chamber syringe.

Examples

[0038] The following examples are illustrative, but do not serve to limit the scope of the invention described herein. The examples are meant only to suggest a method of practicing the present invention.

Example 1: Microparticle preparation

[0039] An appropriate amount of the PLGA polymers is dissolved in an appropriate amount of dichloromethane to give an appropriate polymer concentration as stated in column "PLGA conc." in Table 2. An appropriate amount of drug substance is weight into a glass beaker and the polymer solution is poured over the drug substance so that the resulting microparticles have a drug load as stated in column "drug load".

[0040] E.g. for microparticles with a drug load of 20% and a polymer concentration of 20% the numbers are as the following: 3.547 g of the PLGA polymers are dissolved into 17.7 ml dichloromethane to give a 20 % (w/v) polymer solution. 1.453 g of octreotide pamoate (corresponding to 1.00 g = 20% octreotide free base) is weight into a glass beaker and the polymer solution is poured over the drug substance.

[0041] The suspension is homogenized with an Ultra-Turrax rotor-stator mixer with 20'000 rpm for 1 min under cooling with an ice/water mixture. This suspension is referred to as S/O suspension.

[0042] 10.00 g of Polyvinylalcohol PVA 18-88, 3.62 g KH_2PO_4 and 15.14 g Na_2HPO_4 are dissolved in 2.00 L deionized water to form a 0.5% PVA 18-88 solution buffered to pH 7.4.

[0043] The S/O suspension is mixed with the 0.5 % PVA18-88 solution by pumping the S/O suspension with the help of a flexible tube pump (Perpex, Viton tube) at a rate of 10 ml/min into a turbine and by pumping the aqueous solution with a gear pump (Ismatec MV-Z/B with pumping head P140) at a rate of 200 ml/min into the same turbine. The two solutions are mixed in the turbine at 4'500 rpm. The homogenized S/O/W emulsion is collected into a 2 L glass beaker which is prefilled with 200 ml of the buffered PVA solution.

[0044] The S/O/W emulsion is then heated up to 52°C in 3,5 h - 5 h. The temperature of 52°C is hold for further 30 min - 120 min, before the batch is cooled to room temperature again. During this process escaping dichloromethane is removed by vacuum and the batch is stirred by a 4 blade-propeller-stirrer at 250 rpm.

[0045] As a result, microparticles are formed out of the S/O/W emulsion. The microparticles are collected by filtration (5 μm). They are washed 5 times with 200 ml water and dried for 36 h at 20°C and 0.030 mbar. The dried microparticles are sieved through 140 μm and filled under nitrogen into glass vials. Prepared in that way, the microparticles are sterilized by gamma-irradiation with a dose of 30 kGy.

[0046] The particle size of the microparticles is measured by laser light diffraction. The microparticles are resuspended in white spirit using ultra sound. Table 2 gives the diameter x_{90} (90% of all particles are smaller than this value) after 120 seconds of ultra sound treatment.

[0047] The assay of the microparticles (amount of active ingredient) is determined by HPLC after dissolving the microparticles with ultra sound in a 3:2 mixture of acetonitrile and methanol and further 1:1 dilution with a sodium acetate buffer (pH 4). The solution is cleared from residual particulate matter by centrifugation.

Table 2: Examples 1-1 to 1-82: octreotide pamoate microparticles prepared by one PLGA (reference examples), blends of two PLGAs (reference examples) and microparticle mixtures prepared by microparticles batches with one PLGA only (invention examples).

Ex. Batch	Drug Load (%)	PLGA conc. (%)	A	B	C	D	E	F	G	Process Info	Particle size x_{90} (μm)	Assay (%)
Microparticles with one PLGA in the matrix (Reference Examples)												
1-1	20	20		100						7	46.7	18.6
1-2	20	20			100					7	44.1	18.5
1-3	20	20				100				4	85.7	16.9
1-4	20	20				100				7	73.0	18.6

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Ex. Batch	Drug Load (%)	PLGA conc. (%)	A	B	C	D	E	F	G	Process Info	Particle size X_{90} $\square$ (μm)	Assay (%)
Microparticles with one PLGA in the matrix (Reference Examples)												
1-5	20	20					100			4/38	58.2	9.0
1-6	20	20					100			7	18.4	18.4
Ex. Batch	Drug Load (%)	PLGA conc. (%)	A	B	C	D	E	F	G	Process Info	Particle size X_{90} $\square$ (μm)	Assay (%)
1-7	20	20						100		4	62.3	14.7
1-8	20	20						100		4	85.4	15.7
1-9	20	20						100		7	80.2	17.2
MICROPARTICLE MIXTURES:												
Powder mixtures of microparticles with one PLGA in the matrix (Invention Examples)												
1-10	20	20		30	70					7		18.5
1-11	20	20		10	90					7		18.5
1-12	20	20		50				50		4/7		16.7
1-13	20	20				50		50		4		15.8
POLYMER BLENDS:												
Microparticles with two PLGA polymers in the matrix (Reference Examples)												
1-14	20	20	10	90						7	47.0	18.4
1-15	25	20	10	90						7	56.4	25.4
1-16	20	20	30	70						7	46.4	19.5
1-17	20	20	50	50						7	44.3	20.4
1-18	20	20	10		90					7	44.6	19.3
1-19	20	20	20		80					7	45.2	20.9
1-20	20	20	20			80				4	75.4	14.2
1-21	20	20	10					90		7	67.6	15.5
1-22	20	20	10					90		4	69.4	13.4
1-23	20	25	10					90		4	84.8	14.3
1-24	10	20	20					80		4	63.7	7.0
1-25	15	20	20					80		4	64.7	10.3
1-26	20	20	20					80		4	75.5	14.1
1-27	20	20	20					80		5	67.8	14.2
1-28	25	20	20					80		4	74.6	11.8
1-29	30	20	20					80		4	89.4	10.5
1-30	20	20	30					70		4	59.4	11.5
1-31	20	20		50	50					7	46.3	16.4
1-32	20	20		40	60					7	42.6	18.1
1-33	20	20		30	70					7	51.9	18.9

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(continued)

POLYMER BLENDS: Microparticles with two PLGA polymers in the matrix (Reference Examples)												
1-34	20	25		30	70					7/38	72.6	19.0
1-35	20	20		30	70					7/1:25	53.7	18.9
1-36	20	20		30	70					7/38	49.3	18.5
1-37	20	20		30	70					7/GP	59.6	18.6
Ex. Batch	Drug Load (%)	PLGA conc. (%)	A	B	C	D	E	F	G	Process Info	Particle size $\times_{90}$ $\square$ (μm)	Assay (%)
1-38	20	20		30	70					7/38	52.3	17.9
1-39	15	20		30	70					7	36.2	14.4
1-40	22½	20		30	70					7/38	55.0	19.6
1-41	25	20		30	70					7/38	61.3	21.5
1-42	25	25		30	70					7/38/1:25	75.1	22.5
1-43	20	20		20	80					7	43.4	17.8
1-44	20	20		10	90					7	40.0	18.1
1-45	20	20		50		50				7	61.3	18.9
1-46	20	20		50		50				4	85.9	13.4
1-47	20	25		30		70				4	95.6	17.7
1-48	20	20		30		70				7	59.7	18.6
1-49	20	25		20		80				4	100.5	17.6
1-50	20	20		20		80				4	75.4	15.8
1-51	20	25		10		90				4	105.9	16.9
1-52	20	20		50				50		7	49.5	17.7
1-53	15	20		50				50		7	58.9	13.0
1-54	20	20		50				50		4	58.7	12.1
1-55	20	20		20				80		4	64.0	13.5
1-56	20	20		10				90		4	73.4	14.6
1-57	20	20			50		50			4/38	69.5	12.1
1-58	20	20			90		10			7/38	49.1	16.6
1-59	20	20			70		30			7/38	53.5	18.0
1-60	20	20			50		50			7	37.7	18.3
1-61	20	20			30		70			7/38	52.1	17.1
1-62	20	20				70	30			7	62.8	16.3
1-63	20	20				50	50			7	47.8	16.1
1-64	20	20				30	70			7	50.2	18.1
1-65	20	20			90			10		7/38	50.2	18.9
1-66	20	20			80			20		7	47.2	17.7
1-67	20	20			70			30		7/38	60.2	17.7

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(continued)

Ex. Batch	Drug Load (%)	PLGA conc. (%)	A	B	C	D	E	F	G	Process Info	Particle size x_{90} $\square$ (μm)	Assay (%)
1-68	20	20			50			50		7	58.6	18.6
1-69	20	20			50			50		7/38	65.6	18.3
1-70	20	20			50			50		4	67.4	15.2
1-71	20	20			30			70		4	56.7	11.7
1-72	20	20			20			80		4	77.4	13.2
1-73	20	20			10			90		4	66.5	14.3
1-74	20	20				90		10		7	75.2	18.7
1-75	20	20				70		30		7	88.2	17.1
1-76	20	20				50		50		7	65.1	18.2
1-77	20	20				50		50		4	88.3	16.0
1-78	20	20				30		70		4	75.3	16.0
1-79	20	20				20		80		4	81.9	15.9
1-80	20	20				10		90		4	83.7	16.5
POLYMER BLENDS:												
Microparticles with three PLGA polymers in the matrix (Reference Examples)												
1-81	20	20	15	70					15	7	43.4	19.4
1-82	20	20	15		70				15	7	38.2	18.6
A: star-PLG-D-glucose 50:50 ester 0.3 dL/g (%) B: PLGA 65:35 ester 0.6 dUg (%) C: PLGA 75:25 ester 0.4 dUg (%) D: PLGA 75:25 ester 0.6 dUg (%) E: PLGA 85:15 ester 0.4 dUg (%) F: PLGA 85:15 ester 0.6 dUg (%) G: PLA 100:0 acid 0.2 dL/g (%)												

Process Info = Further Process Information:

[0048]

7: 66 mM PBS pH 7.4
5: 69 mM Citrate-phosphate buffer pH 5.0
4: 69 mM Citrate-phosphate buffer pH 4.0
38: Turbine speed 3800 rpm instead of 4500 rpm
1:25: Flowrate ratio SO/W = 1:25 instead of 1:20
GP: Gear pump instead of peristaltic pump

Example 2: Vehicle compositions A to G

[0049] CMC-Na, Mannitol and Pluronic F68 in an amount as given in Table 3 are dissolved in about 15 ml hot deionized water of a temperature of about 90°C under strong stirring with a magnetic stirrer. The resulting clear solution is cooled to 20°C and filled up with deionized water to 20.0 ml.

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Table 3: Suitable vehicles for the microparticles (Amounts given in g)

	A	B	C	D	E	F	G
CMC-Na	0	0	0.05	0.14	0.28	0.35	0.40
Mannitol	0	1.04	0.99	0.90	0.76	0.74	0.68
Pluronic F68	0.04	0.04	0.04	0.04	0.04	0.04	0.04

Example 3: Microparticle suspension

[0050] 170 mg of microparticles of example 1-33 are suspended in 1.0 ml of a vehicle of composition D (Table 3) in a 6 R vials. The suspensions are homogenized by shaking for about 30 seconds by hand. The reconstituted suspension may be injected without any issues using a 20 Gauge needle.

Example 4: Lyophilisation of the microparticles

[0051] 170 mg of microparticles of example 1-33 are reconstituted in 1 ml of the vehicle composition F (Table 3), homogenized by stirring for 1 to 12 hours and then freeze-dried in a lyophilisator. Reconstitution of the lyophilized microparticles with 1 ml pure water (aqua ad injectabilia) resulted in fast and good wetting of the microparticles that may be injected without any issues using a 20 Gauge needle.

Example 5: Release profile in vivo (rabbits)

[0052] Microparticles containing octreotide are suspended in 1 ml of a suitable aqueous vehicle, preferably in vehicle D, and the resulting suspension is injected intramuscularly (i.m.) into male New Zealand White bastard rabbits in a dose of 4 mg/kg. For each dosage form (test group) 4 animals are used. After defined time periods (indicated in the table 4) plasma samples are taken and analyzed for octreotide concentration.

Table 4: Plasma levels (dose corrected values); concentration in ng/ml

Ex. Batch	Time after Administration (days)											
	0.021	0.042	0.083	0.167	0.250	1	2	3	5	8	12	
1-10	9.653	9.245	4.201	1.159	0.402	0.000	0.000	0.205	0.888	1.216	0.954	
1-33*	22.735	16.333	6.359	1.621	0.575	0.017	0.085	0.318	1.081	1.249	1.088	
1-68	3.622	4.099	2.748	0.939	0.440	0.028	0.000	0.085	0.377	0.690	0.575	
1-44	5.675	4.460	1.799	0.522	0.175	0.000	0.000	0.103	0.695	0.918	0.785	
1-33	21.071	19.719	9.704	2.852	1.121	0.155	0.334	0.858	2.240	2.868	3.093	
1-40	1.047	1.032	0.856	0.350	0.182	0.000	0.000	0.188	1.252	1.374	1.169	
1-48	0.662	0.645	0.494	0.248	0.123	0.000	0.000	0.108	0.751	0.992	0.901	
1-67	0.952	0.928	0.672	0.232	0.094	0.000	0.000	0.096	0.448	0.609	0.519	
1-82	31.669	31.171	22.023	9.302	3.985	0.411	0.417	0.425	0.209	0.219	0.247	
1-22	3.973	15.301	17.168	13.803	10.187	0.944	0.270	0.283	0.946	1.684	0.527	
1-26	3.799	13.875	17.515	14.105	11.060	0.697	0.164	0.271	0.535	1.491	1.505	
19	27	33	40	47	54	61	68	75	82	89	96	
1-10	0.911	0.513	0.343	0.222	0.600	0.706	0.578	0.705	0.622	0.623	0.219	0.054
1-33*	0.867	0.477	0.227	0.127	0.545	0.579	0.843	1.169	0.439	0.146	0.019	0.000
1-68	0.509	0.435	0.494	0.408	0.317	0.243	0.152	0.165	0.424	0.621	0.765	0.640
1-44	0.626	0.367	0.244	0.106	0.060	0.233	0.648	1.023	1.046	0.505	0.155	0.000
1-33	2.254	1.957	0.779	0.366	0.340	1.461	3.024	3.358	2.405	0.928	0.391	0.125
1-40	0.948	0.690	0.299	0.164	0.528	1.585	1.225	0.714	0.505	0.284	0.070	0.000

(continued)

19	27	33	40	47	54	61	68	75	82	89	96	
1-48	0.557	0.498	0.387	0.254	0.114	0.171	0.846	1.058	1.935	0.693	0.359	0.180
1-67	0.482	0.440	0.378	0.253	0.175	0.106	0.096	0.152	0.446	0.534	0.542	0.462
1-82	0.286	0.275	0.137	0.135	0.147	0.254	0.350	0.570	0.442	0.320	0.162	0.039
1-22	0.631	1.077	0.510	0.362	0.189	0.129	0.227	0.140	0.281	0.227	0.141	0.073
1-26	0.494	0.468	0.354	0.262	0.286	0.213	0.530	0.424	0.311	0.148	0.115	0.108
* Dose = 12 mg/kg												

Claims

1. A sustained release pharmaceutical composition in form of microparticles comprising as active ingredient octreotide or a pharmaceutically-acceptable salt thereof and two or more different polylactide-co-glycolide polymers (PLGAs), wherein the PLGAs are present in a mixture of depots which is a mixture of two or more depots like microparticles of different composition with one and more PLGAs in each depot, and wherein the PLGAs have a lactide:glycolide monomer ratio of 100:0 to 40:60 and the inherent viscosity of the PLGAs is below 0.9 dl/g in chloroform.
2. The pharmaceutical composition according to any one of the claim 1 wherein at least two PLGAs are linear.
3. The pharmaceutical composition according to any one of the claims 1 to 2 comprising the pamoate salt of octreotide.
4. The pharmaceutical composition according to any one of the claims 1 to 3 wherein the release of the active ingredient is three or more months.
5. The pharmaceutical composition according to claim 1 wherein the microparticles have a diameter between 10 μm and 90 μm .
6. The pharmaceutical composition according to claim 1 or 5 wherein the microparticles are additionally mixed, covered or coated with an anti-agglomerating agent.
7. The pharmaceutical composition according to claim 6 wherein the anti-agglomerating agent is mannitol.
8. The pharmaceutical composition according to any one of the claims 1 to 7 sterilized by gamma irradiation.
9. Pharmaceutical composition according to any one of the claims 1 to 8 for use in long-term maintenance therapy in acromegalic patients, and treatment of severe diarrhea and flushing associated with malignant carcinoid tumors and vasoactive intestinal peptide tumors (vipoma tumors).
10. An administration kit comprising the pharmaceutical composition according to any one of the claims 1 to 9 in a vial, together with a water-based vehicle in an ampoule, vial or prefilled syringe or as microparticles and vehicle separated in a double chamber syringe.

Patentansprüche

1. Pharmazeutische Zusammensetzung mit anhaltender Freisetzung in Form von Mikropartikeln, umfassend Octreotid oder ein pharmazeutisch unbedenkliches Salz davon als Wirkstoff und zwei oder mehr verschiedene Polylactid-Co-Glycolid-Polymere (PLGAs), wobei die PLGAs in einer Mischung von Depots vorliegen, bei der es sich um eine Mischung von zwei oder mehr Depots ähnlicher Mikropartikel verschiedener Zusammensetzung mit einem oder mehreren PLGAs in jedem Depot handelt und wobei die PLGAs ein Lactid:Glycolid-Monomerverhältnis von 100:0 bis 40:60 aufweisen und die inhärente Viskosität der PLGAs in Chloroform unter 0,9 dl/g liegt.
2. Pharmazeutische Zusammensetzung nach Anspruch 1, wobei mindestens zwei PLGAs geradkettig sind.

3. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 2, umfassend das Pamoatsalz von Octreotid.
4. Pharmazeutische Zusammensetzung nach einem der Ansprüche 1 bis 3, wobei die Freisetzung des Wirkstoffs über drei oder mehr Monate stattfindet.
5. Pharmazeutische Zusammensetzung nach Anspruch 1, wobei die Mikropartikel einen Durchmesser zwischen 10 μm und 90 μm aufweisen.
6. Pharmazeutische Zusammensetzung nach Anspruch 1 oder 5, wobei die Mikropartikel zusätzlich mit einem Antiagglomerationsmittel gemischt, beschichtet oder überzogen sind.
7. Pharmazeutische Zusammensetzung nach Anspruch 6, wobei es sich bei dem Antiagglomerationsmittel um Mannitol handelt.
8. Pharmazeutische Zusammensetzung nach einem der Ansprüche 1 bis 7, sterilisiert durch Gammastrahlung.
9. Pharmazeutische Zusammensetzung nach einem der Ansprüche 1 bis 8 zur Verwendung bei der langfristigen Erhaltungstherapie von Akromegaliepatienten und der Behandlung von schwerem Durchfall und Hitzewallungen, die mit malignen karzinoiden Tumoren und Vasoaktivesintestinales-Peptid-Tumoren (VIPom-Tumoren) assoziiert sind.
10. Verabreichungskit, umfassend die pharmazeutische Zusammensetzung nach einem der Ansprüche 1 bis 9 in einem Vial zusammen mit einem Vehikel auf Wasserbasis in einer Ampulle, einem Vial oder einer vorgefüllten Spritze oder als Mikropartikel und Vehikel getrennt in einer Doppelkammerspritze.

Revendications

1. Composition pharmaceutique à libération prolongée sous forme de microparticules comprenant, en tant que substance active, de l'octréotide ou un sel pharmaceutique acceptable de celui-ci et deux polymères polylactide-coglycolide (PLGA) ou plus différents, dans laquelle les PLGA sont présents dans un mélange de formulations retard qui est un mélange de deux formulations retard ou plus telles que des microparticules de composition différente avec un ou plusieurs PLGA dans chaque formulation retard, et dans laquelle les PLGA présentent un rapport de monomère lactide:glycolide de 100:0 à 40:60 et la viscosité intrinsèque des PLGA est inférieure à 0,9 dl/g dans du chloroforme.
2. Composition pharmaceutique selon la revendication 1, dans laquelle au moins deux PLGA sont linéaires.
3. Composition pharmaceutique selon l'une quelconque des revendications 1 et 2, comprenant le sel de pamoate d'octréotide.
4. Composition pharmaceutique selon l'une quelconque des revendications 1 à 3, dans laquelle la libération de la substance active est de trois mois ou plus.
5. Composition pharmaceutique selon la revendication 1, dans laquelle les microparticules ont un diamètre compris entre 10 μm et 90 μm .
6. Composition pharmaceutique selon la revendication 1 ou 5, dans laquelle les microparticules sont en outre mélangées, revêtues ou enrobées avec un agent antiagglomérant.
7. Composition pharmaceutique selon la revendication 6, dans laquelle l'agent antiagglomérant est le mannitol.
8. Composition pharmaceutique selon l'une quelconque des revendications 1 à 7, stérilisée par irradiation gamma.
9. Composition pharmaceutique selon l'une quelconque des revendications 1 à 8, pour utilisation dans une thérapie d'entretien à long terme chez des patients acromégaliques, et dans le traitement d'une diarrhée sévère et des bouffées congestives associées à des tumeurs épidermoïdes malignes et des tumeurs à peptide vasoactif intestinal (tumeurs de type vipome).

- 10.** Trousse d'administration comprenant la composition pharmaceutique selon l'une quelconque des revendications 1 à 9 dans un flacon, conjointement avec un véhicule à base d'eau dans une ampoule, un flacon ou une seringue préremplie ou sous forme de microparticules et un véhicule séparé dans une seringue à chambre double.

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REFERENCES CITED IN THE DESCRIPTION

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